

REVIEW

The role of radiology in paediatric soft tissue sarcomas

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Abstract

Paediatric soft tissue sarcomas (STS) are a group of malignant tumours that originate from primitive mesenchymal tissue and account for 7% of all childhood tumours. Rhabdomyosarcomas (RMS) and undifferentiated sarcomas account for approximately 50% of soft tissue sarcomas in children and non-rhabdomyomatous soft tissue sarcomas (NRSTS) the remainder. The prognosis and biology of STS tumours vary greatly depending on the age of the patient, the primary site, tumour size, tumour invasiveness, histologic grade, depth of invasion, and extent of disease at diagnosis. Over recent years, there has been a marked improvement in survival rates in children and adolescents with soft tissue sarcoma and ongoing international studies continue to aim to improve these survival rates whilst attempting to reduce the morbidity associated with treatment. Radiology plays a crucial role in the initial diagnosis and staging of STS, in the long term follow-up and in the assessment of many treatment related complications. We review the epidemiology, histology, clinical presentation, staging and prognosis of soft tissue sarcomas and discuss the role of radiology in their management.

Keywords: *Rhabdomyosarcoma; paediatric soft tissue sarcoma; diagnostic imaging; non-rhabdomyomatous soft tissue sarcoma.*

Introduction

Soft tissue sarcomas (STS) are a group of neoplasms originating from primitive mesenchymal tissue which represent 7% of all childhood tumours. They are classified into two groups, rhabdomyosarcomas (RMS), which account for approximately 50% of paediatric STS and a variety of non-rhabdomyomatous STS (NRSTS) which make up the remainder. NRSTS are a heterogeneous group of tumours which include neoplasms of smooth muscle (leiomyosarcoma), connective tissue (fibrous and adipose), vascular tissue (blood and lymphatic vessels), and the peripheral nervous system (Table 1). Synovial sarcomas, fibrosarcomas, malignant fibrous histiocytoma (MFH) and neurofibrosarcomas predominate in paediatric patients.

Soft tissue sarcomas have become increasingly curable over the past quarter of a century; the cure rate for rhabdomyosarcoma was only 25% in 1970 compared to 70% in 1991^[1]. Improved outcome is a result of increasingly effective multimodal therapy, better supportive care

and refinements in tumour grouping and staging. Radiology plays a crucial role in the initial staging of children with STS, in their long term follow-up and in assessment of the not infrequent treatment-related complications.

Table 1 *Histological classification of non-rhabdomyomatous soft tissue sarcomas*

More common histology	Less common histology
Dermatofibrosarcoma protruberans	Alveolar soft part sarcoma
Desmoid-type fibromatoses	Angiosarcoma of soft tissue
Fibrosarcoma – infantile type	Clear cell sarcoma of soft tissue
Inflammatory myofibroblastic tumour	Epithelioid sarcoma
Leiomyosarcoma	Fibrosarcoma – adult type
Liposarcoma	Haemangiopericytoma
Malignant fibrous histiocytoma	Mesenchymal chondrosarcoma
Malignant peripheral nerve sheath tumour	
Rhabdoid tumour	
Synovial sarcoma	

Prognosis varies greatly depending on tumour site, surgical resectability, tumour size, invasiveness, histology and grade and the age of the patient. There have been conflicting reports as to whether age of less than 12 months at the time of diagnosis is a poor or favourable prognostic factor. A recent report from the Society of Paediatric Oncology (SIOP) group reviewed 102 infants diagnosed with STS within the first year of life and found that, despite the necessary limitations concerning intensity of treatment in these patients, outcome was as satisfactory as that achieved in older children. The outcome for infants with alveolar RMS and metastatic disease was poor, as it is for older children and these patients require intensified chemotherapy regimes and aggressive local treatment^[21].

Rhabdomyosarcoma

Epidemiology and histology

Rhabdomyosarcoma is the most common soft tissue sarcoma in children under the age of 15 years and is the third most common extracranial solid childhood tumour after neuroblastoma and Wilms' tumour, accounting for approximately 4% of malignancies in childhood^[3]. Almost two-thirds of all cases are diagnosed in children aged 6 years or younger with a smaller incidence peak in early to mid adolescence.

RMS arises from immature mesenchymal cells committed to skeletal cell lineage but may arise anywhere in the body, often in sites lacking striated muscle, for example, the urinary bladder. It is a typical small, round, blue-cell tumour on conventional histology, and is classified histologically using the International Classification of RMS^[4] which is based on the relationship between prognosis and histology. Histologically, the presence of myofibrils and cross striations and/or a positive immunohistochemical staining for markers of muscle differentiation like desmin and myoD1 is essential in the diagnosis of RMS.

There are four subtypes of tumour: undifferentiated sarcoma and alveolar RMS (ARMS), which both have poorer prognosis, embryonal RMS (ERMS) which has an intermediate prognosis and other botryoid and spindle-cell RMS, less common variants of ERMS, which have the best prognosis. Botryoid RMS is seen almost exclusively in the bladder or vagina of infants or young girls or the nasopharynx of slightly older children and has a particularly favourable prognosis, rarely metastasising and responding well to current treatment regimes. Of newly diagnosed RMS, 60% are of the embryonal subtype and 20% alveolar^[3]. ARMS is more aggressive than ERMS and has a worse prognosis. Results from the Intergroup Rhabdomyosarcoma Study (IRS) I–III studies gave a 94% 5-year survival for orbital ERMS versus a 74% 5-year survival for orbital ARMS for example^[5].

The genetic changes associated with RMS differ with histotype. ARMS is associated with t(2;13)(q35) or t(1;13)(p36;q14) chromosomal translocations which cause rearrangement of transcription factors (generating PAX3-FKHR and PAX7-FKHR fusion products) and ultimately result in modification of cell growth, differentiation and apoptotic pathways. In contrast, most ERMS tumours have allelic loss at chromosome 11p15.5. Studies demonstrate repression of tumour growth from this chromosomal region, suggesting the presence of a tumour suppressor gene. In both ERMS and ARMS, common targets are affected, such as the p53 and RB pathways^[6].

The majority of cases are sporadic but there is an association with certain familial syndromes such as Li–Fraumeni syndrome, which includes RMS and other soft tissue sarcomas, and has been associated with germline mutations of the p53 tumour suppressor gene^[7].

Clinical presentation, anatomical location and patterns of spread

In the majority of patients presentation is either the discovery of a mass lesion in any body region or with disturbance of body function by the enlarging tumour or involved lymph nodes^[8] (Fig. 1). Anatomical location, as reported from the first three IRS trials was 35–40% head and neck, 25% genitourinary tract, 20% extremities, 10% truncal and 10% other sites.

The head and neck tumours were 50% parameningeal, 25% orbital and 20% other head and neck sites^[9]. Orbital primaries present with proptosis or, occasionally,

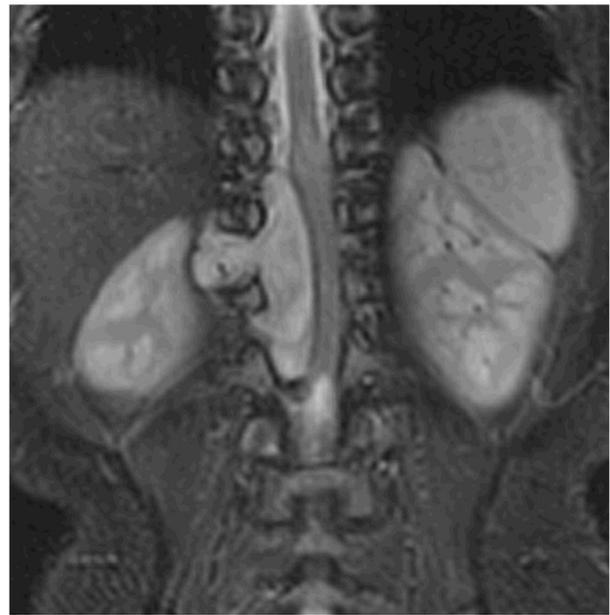


Figure 1 Coronal T2 weighted MRI showing a thoracolumbar dumbbell-shaped RMS causing compression of the spinal cord.

ophthalmoplegia and are, therefore, usually diagnosed before distant dissemination. Regional lymphadenopathy is unusual which may be secondary to the poor lymphatic supply to the orbit.

Non-orbital parameningeal primaries can present with nasal, aural or sinus obstruction or discharge with cranial nerve palsy suggesting extension towards the meninges. Headache, vomiting and raised intracranial pressure can be seen with intracranial growth. Metastases occur to lung and bones. Other head and neck tumours tend to present as painless masses increasing in size and often remain localised^[10].

Genitourinary tract RMS is seen most commonly in the bladder and prostate and the alveolar histotype is uncommon in this location^[11]. Bladder RMS is often polypoid and tends to grow intraluminally in or near the trigone, presenting with haematuria or obstruction and, occasionally, mucosanguinous tissue extrusion. Children are usually under 4 years of age at presentation and the tumours tend to remain localised. Prostate RMS however presents as a large pelvic mass sometimes with urinary retention or constipation. Infants or older children are affected and dissemination to lung, bone marrow or bones often occurs early^[11]. Vaginal RMS is almost invariably botryoid and affects very young girls as described earlier. Cervical and uterine RMS are seen more commonly in older girls and present with a mass or discharge^[8,12]. Regional lymph node involvement is uncommon.

Paratesticular RMS presents as a painless, unilateral scrotal or inguinal enlargement and is seen in both pre- and postpubertal boys. Under 10 years old, retroperitoneal lymph node involvement is rare, but is seen in up to 50% of older boys. Distant metastases are seen in 10–20%, mostly to lung and cortical bone^[13].

RMS in the extremities presents primarily as a swelling which may or may not be tender, painful or erythematous. In 50–75% of cases, there is an alveolar histotype and regional lymph node involvement is present in under 50% at presentation, being more common in ARMS than ERMS or undifferentiated RMS. The tumours can be extensive as they tend to spread along the facial planes. A history of injury to the extremity, which is common in school-aged children, can lead to delayed diagnosis^[14].

All RMS histotypes are seen in the trunk and the tumours tend to recur locally despite wide local excision. Distant spread is common and they are often large at the time of diagnosis. Spread to the thoracolumbar spine may occur but regional lymphadenopathy is unusual.

Intrathoracic, retroperitoneal and pelvic primaries are often large at the time of diagnosis with complete surgical resection being difficult due to tumour surrounding vital vessels. There is, therefore, an increased risk of local recurrence despite combined modality treatment^[15]. Perineal and perianal RMS is unusual and may mimic an abscess or polyp. They are often alveolar with a relatively high degree of lymph node involvement^[16].

Biliary tract RMS is even rarer and may present with obstructive jaundice. Spread occurs locally, within the liver and then to the retroperitoneum or lungs. Aggressive surgical resection may be less important in determining a favourable outcome in this location^[17]. Unusual primary sites include liver, brain, trachea, heart, breast and ovary. Metastatic RMS with unknown primary has also been described^[18].

Staging and prognosis

A number of different staging systems have been used by various cooperative paediatric oncology groups worldwide, the majority being post-surgical systems based on tumour resectability. More recently, for the Intergroup Rhabdomyosarcoma Study IV, a pre-treatment, site-modified TNM staging system (stages I–IV) was developed^[19] and used in conjunction with the Children's Oncology Group surgicopathological staging system which classifies patients as Clinical Group (CG) I–IV on the basis of tumour resectability. Both stage and group were shown to be highly predicative of outcome and were highly correlated^[19,20].

The site-modified TNM system divides patients into favourable and unfavourable sites but has been abandoned by the Society of Paediatric Oncology (SIOP) in favour of the IRS grouping system.

There is ever increasing use of and reliance on imaging techniques, in particular computed tomography (CT) and magnetic resonance imaging (MRI) which should facilitate a better assessment of tumour extent at diagnosis, including the demonstration of enlarged regional lymph nodes (and presumed tumour involvement). Apart from two exceptions, physical examination and imaging studies are adequate for establishing regional lymph node involvement, precluding the need for routine surgical sampling of 'benign' nodes. The exceptions are in extremity RMS and paratesticular RMS (in which, as an exception to the rule, ultrasound (US) is the imaging modality of choice) in boys of 10 years or over, in whom aggressive sampling of regional nodal basins and ipsilateral lymph nodes respectively, should be undertaken due to the high incidence of regional nodal metastases^[21].

Favourable prognosis factors for RMS are: (i) the absence of metastases at diagnosis; (ii) favourable tumour site; (iii) grossly complete surgical removal of localised tumour at the time of diagnosis; (iv) embryonal or botryoid histology; (v) tumour size of less than or equal to 5 cm; and (vi) age of younger than 10 years at diagnosis (Table 2)^[22,23].

The reported cure rate for RMS is currently approximately 70%. Based on the IRS IV study, the predicted 5-year failure free survival rate for low risk patients is 88%, for intermediate risk patients is 70% and for those with metastatic disease is 25%. This final high-risk group comprises less than 20% of all patients^[24].

Non-rhabdomyomatous soft tissue sarcomas

Epidemiology, histology and genetics

Approximately 50% of paediatric soft tissue sarcomas are non-rhabdomyomatous soft tissue sarcomas (NRSTS) accounting for about 3% of childhood malignancies. They are a heterogeneous group of tumours, all of mesenchymal origin, that share some biological characteristics but differ histologically. The most common NRSTS are synovial cell carcinoma (17–42%), fibrosarcoma (13–15%), malignant fibrous histiocytoma (12–13%) and malignant peripheral nerve sheath tumours (10%)^[25–27]. Other histological types include epithelioid sarcoma, malignant neurogenic tumours, haemangiopericytomas, alveolar soft part sarcomas, leiomyosarcomas, liposarcomas and desmoplastic small cell tumours (Table 2).

The incidence of some histological subtypes is age dependent, with fibrosarcomas occurring more commonly in children under 1 year old and synovial

sarcomas and malignant peripheral nerve sheath tumours (MPNST) being more common in children over 10 years old.

The clinical behaviour and outcomes of NRSTS in children are often very different to those in adults and, particularly in infants and young children, prognosis is generally better. Examples of this different natural history include infantile fibrosarcoma and haemangiopericytoma which, unlike the adult tumours, rarely metastasize and are generally cured if complete surgical removal is achieved. Adolescent NRSTS, however, tend to behave more like those seen in adults^[28,29].

The vast majority of cases of NRSTS are sporadic and, as with RMS, many have been shown to have specific chromosomal translocations, for example, t(X;18) (p11;q11) occurs in >90% of synovial sarcomas^[30]. There are familial associations, NRSTS occurring in patients with Li–Fraumeni syndrome as well as in neurofibromatosis type 1. The latter is strongly associated with the development of MPNSTs. Genetic studies suggest loss of heterozygosity of a tumour suppressor gene or genes within the tumour cells.

Table 2 *EpSSG prognostic factors*

	Favourable	Unfavourable
Histology	Embryonal	Alveolar
IRS Group	Higher grades more unfavourable	
Tumour site	Head and neck, non-parameningeal; orbital; genitourinary, non-bladder/prostate	All other sites
Node involvement	N ₀	N ₁
Tumour size	≤5 cm	>5 cm
Age	<10 years of age	≥10 years of age

Clinical presentation, anatomical location and patterns of spread

NRSTS can arise anywhere in the body but are most common in the extremities and trunk^[25]. Presentation is usually with a painless mass but symptoms may occur secondary to local invasion or mass effect (Fig. 2). Systemic symptoms such as fever, night sweats or weight loss are rare but have been observed with widespread metastatic disease. MPNST may present with motor and sensory involvement. Rarely patients may present with metabolic disturbances^[31,32]. Dillon *et al.*^[25] looked at the anatomical location of a cohort

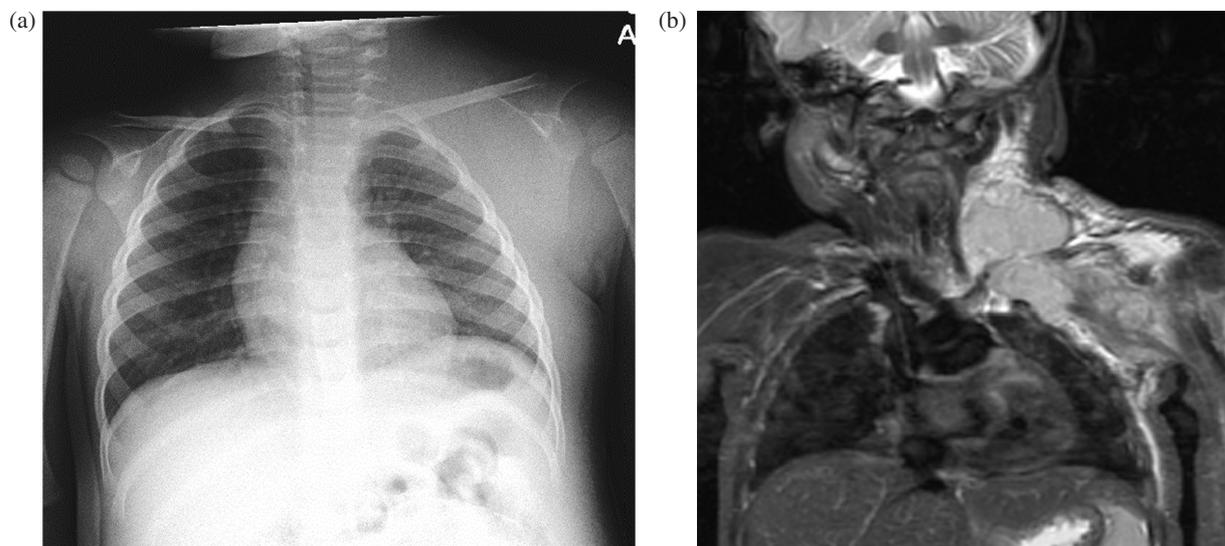


Figure 2 (a) Chest X-ray demonstrating a rhabdoid tumour involving the soft tissues of the left side of the neck and chest wall. (b) Coronal T2 weighted MRI of the same patient.

of 75 cases of paediatric NRSTS and found 65% in the extremities, 28% in the trunk and 7% in the head and neck. Metastases at time of presentation were more common in the truncal tumours than those in the extremities. All upper limb tumours were localised at the time of presentation, whereas 78% of abdominal tumours had metastatic disease at the time of presentation.

Estimates of the proportion of children with metastases at diagnosis vary from 5%^[26] to about 15%^[33]. Pulmonary metastases are the most common site, followed by bone, liver and mesenteric metastases. Lymphatic spread is rare, particularly in tumours in the extremities where it is approximately 4%^[14] but is seen more commonly with high grade lesions such as synovial sarcoma, angiosarcoma and epithelioid sarcoma.

Staging and prognosis

There are a number of different staging systems in use for paediatric NRSTSs but traditionally staging has been according to the Intergroup Rhabdomyosarcoma Study Group surgicopathological system, as used for rhabdomyosarcomas^[34]. Histological grade is also used in clinical staging as it is highly predictive of clinical outcome^[35].

Assessments of percentage of cases presenting with metastatic disease vary widely from as little as 5% to as much as 30%^[25,26]. Risk factors for local recurrence differ from those for distant recurrence^[36]. Local recurrence is predicted by positive surgical margins, intra-abdominal primary tumour site and the omission of radiotherapy. Distant recurrence is predicted by tumour size (5 cm or more), invasiveness and high grade.

The most important prognostic factor seems to be complete surgical removal of the tumour with 5-year survival of 84–9% with complete resection and only 30–50% with incomplete resection or metastases at presentation. Children in whom complete resection was achieved had a local recurrence rate of 12.8% and a distant recurrence rate of 11.8% at 5 years^[33,36].

Several reports have shown a prolonged survival after surgical treatment of pulmonary metastases from soft tissue sarcoma. Prognosis is better in grade I and II tumours and if complete resection of the metastases is achieved^[37].

Common paediatric non-rhabdomyomatous soft tissue sarcomas

Synovial cell carcinoma

Synovial sarcoma is the most common NRSTS in adolescents and young adults. The median age of presentation is 13 years old and 60–74% present in the lower extremity, often around the thigh or knee^[38] with the upper extremity being the next most common site of occurrence.

Five to 12 percent have metastases at presentation and of these, 94% are pulmonary^[25]. Five-year survival is 80% with grade I and II tumours but only 17% with grades III and IV^[39]. Treatment is with wide local excision with or without radiotherapy. The role of chemotherapy has not been established.

Fibrosarcoma

Fibrosarcoma makes up 13–15% of childhood NRSTS and is the most common in infants under 1 year old (infantile fibrosarcoma)^[27]. A second peak is seen in the 10–15 year old age group. The infantile form, despite looking identical histopathologically, demonstrates a more benign course than that in older children and rarely metastasises even in cases with repeated local recurrence. Treatment is therefore often confined to wide local excision without any radiotherapy or chemotherapy. Spontaneous regression is also recognised, albeit difficult to predict. However, with large masses, preoperative chemotherapy has been shown to reduce mass size allowing more conservative surgery^[40]. Retroperitoneal and head and neck lesions fare worse than extremity lesions with metastases developing in 26% compared with 10% in the extremities^[28]. Metastases are seen more frequently in postpubertal children, most commonly pulmonary.

Malignant fibrous histiocytoma

Malignant fibrous histiocytoma (MFH) can occur anywhere in the body but is more common in the extremities. It makes up 12–13% of childhood NRSTSs. It rarely occurs in the neonatal period or during the first year of life^[27]. Microscopically, MFH resembles fibrosarcoma but has a number of distinctive features which include the presence of marked cellular pleomorphism, the presence of multiple cell types and a generally more malignant appearance. The distinction of MFH from fibrosarcoma recurrence can be difficult.

Angiomatoid MFH is the only common form of MFH occurring as a primary tumour in children (especially those under 15 years old) and ongoing work suggests that it should be differentiated from adult-type MFH. Angiomatoid MFH has a very favourable prognosis with only 1% of tumours developing metastases. MFH is one of the most common radiation-induced sarcomas. The most common site of metastasis is to the lung, although metastases to the brain and other sites are also seen. Patients with tumours in the extremities have a better 3-year survival than those of the trunk or head and neck (81% vs 54% respectively)^[41]. Initial management is with wide local excision alone, particularly with angiomatoid MFH, however, the tumour does appear to be chemosensitive and the use of adjuvant chemotherapy is being further evaluated.

Malignant peripheral nerve sheath tumour

Malignant peripheral nerve sheath tumour (MPNST) accounts for approximately 5–10% of childhood NRSTSs. It occurs in association with NF1 with approximately 5–16% of patients with NF1 developing MPNST. Genetic data suggests the loss of a tumour suppressor gene on chromosome 17 is important in the pathogenesis of the tumour. The tumour has a variety of histological appearances and again, has a superficial resemblance to fibrosarcoma.

In a report of 24 children with MPNST, 16 had the associated neurofibromatosis syndrome. The most common primary sites were extremity (42%), reprotoitoneum (25%) and trunk (21%). Metastases are seen in about 12% of patients at diagnosis.

Surgical excision plays a key role in management. Approximately 75% of patients in whom gross surgical resection is possible remain disease free at 3 years with less than a third of patients in whom gross surgical resection is not possible remaining disease free at 3 years. Patients treated with gross resection and irradiation to microscopic residual disease had a similar good outcome to those with complete excision with disease-free margins. The role of chemotherapy in MPNST is not yet established and although it has been shown to produce tumour regression in metastatic disease, results for disease-free survival in patients with advanced disease are poor^[27].

Imaging recommendations

Imaging plays an essential role at the time of presentation, both as an aid to diagnosis and also to assess tumour size, relation to or involvement of adjacent structures and to look for evidence of local and distant spread. Imaging of the primary site should be performed with US first for abdominal and superficial masses. Inevitably CT or MRI will also be required, both with intravenous contrast administration, with measurement of the tumour recorded in at least the two largest dimensions^[42]. Paediatric investigators often advocate a volume estimation for assessing tumour size and response to treatment. The new European Pediatric Soft Tissue Sarcoma study group (EpSSG) will assess response with volume measurements but also plans to retrospectively assess response with unidimensional measurements as recommended by the Response Evaluation Criteria in Solid Tumours (RECIST) guidance. MRI is recommended for limb, pelvic and paraspinal masses with CT being superior in evaluation of possible bone erosions and abdominal lymphadenopathy. Occasionally, ultrasound may be the imaging modality of choice, for example, in the staging and assessment of local disease in paratesticular RMS.

Treatment response should ideally be assessed using the same imaging modality as the initial assessment, however, if the original imaging modality used was CT,

follow-up with MRI may be thought preferable to try and limit the use of ionising radiation. Limiting the use of ionising radiation is of importance to try and reduce the risk of radiation induced cancers; this is particularly so in a group of children who have already presented with malignancy early in life. Whichever modality is used, it is important to reassess the tumour using the same measurement parameters as before. This is particularly true of MRI, such that the same planes and sequences should be used on follow-up whenever possible.

Imaging of the primary site should include assessment of the regional lymph nodes particularly as routine lymph node sampling at surgery is not advocated in the majority of cases. For limb tumours the regional nodes include the axilla and inguinal regions and these must be evaluated by US in addition to MRI of the primary site.

Approximately 15% of paediatric STSs will have metastatic disease at presentation. Pulmonary metastases are seen in at least 8% of patients with RMS at presentation, including those with a negative chest radiograph^[42] and a chest CT is therefore recommended in all patients. The majority of imaging protocols for STS include Tc99mMDP bone scintigraphy at diagnosis to look for skeletal metastases. However, in some soft tissue sarcomas only a small percentage of these scans are positive. In addition, all bone metastases are not evident on bone scintigraphy^[43]. Studies do, however, suggest that bone scans are more reliable than skeletal surveys for RMS^[44]. To reduce the trauma to the child and the overall cost of staging it may be advisable to limit bone scintigraphy to patients with unfavourable histology or bone pain^[45]. An alternative in the future may be the introduction of whole body MRI or positron emission tomography (PET)-CT as a means of detecting distant metastases.

The role of PET-CT in paediatric STSs is as yet unclear. Early reports suggest it may be a helpful adjunct in monitoring response to treatment. It has shown to be of use in the identification of unknown primary rhabdomyosarcoma and detection of unsuspected and unusual metastatic sites of disease in various childhood sarcomas. It has shown variable specificity as a marker of nodal disease^[46].

Table 3 summarises the major imaging features of soft tissue sarcomas which are further described below.

RMS imaging by anatomic location

Head and neck

RMS of the head and neck grows insidiously and often invades the intracranial space through the numerous foramina leading to the brain. Imaging using MRI is mandatory because of the capability of assessing local and intracranial extension. It typically has a loose stromal network and high overall water content resulting in high signal intensity on long TR/TE images. The masses are

Table 3 The major imaging features of soft tissue sarcomas

	Imaging findings
Rhabdomyosarcoma	
Head and neck	High signal on T2; isointense to muscle on T1; often invade intracranial space; parameningeal tumours tend to be large and invasive
Orbital	Generally confined to bony orbit; intra- or extraconal; regional lymphadenopathy is rare
Abdomen	May metasasise to liver or peritoneal surfaces; biliary RMS causes biliary dilatation and a hilar mass; may extend into the duodenum
Genitourinary	Prostatic tumours commonly spread laterally and posteriorly often invading the bladder base; pre- and post-contrast coronal and sagittal T1 images useful in assessing spread; paratesticular RMS has non-specific findings on US with variable echogenicity and heterogeneity; may show increased flow and low resistance on Doppler; abdominal CT advised due to high incidence of lymph node involvement
Extremities	Fat suppressed coronal images demonstrate the supero-inferior extent of the tumour and regional lymphadenopathy; all limb nodal stations should be evaluated
NRSTS	
Synovial sarcoma	On MR, tumour appears sharply margined and largely cystic; 'triple sign' seen in about 33%; fluid-fluid levels in 18%; tumours <5 cm are typically homogeneously low on T1 and heterogeneous on T2; 75% intimately related to bone; 30% contain calcification
Fibrosarcoma	Soft tissue mass with non-specific imaging features; medium signal intensity on T1, high on T2 with inhomogeneous enhancement; solid, vascular mass on US
MFH	Well-defined, heterogeneous intramuscular mass; usually low to intermediate signal on T1, intermediate to high on T2; calcification may occur; solid components reveal nodular and peripheral enhancement
MPNST	Low density on unenhanced CT; isointense to muscle on T1, hyperintense on T2 with moderate to marked enhancement; 'target sign' much more common in neurofibromas than MPNSTs

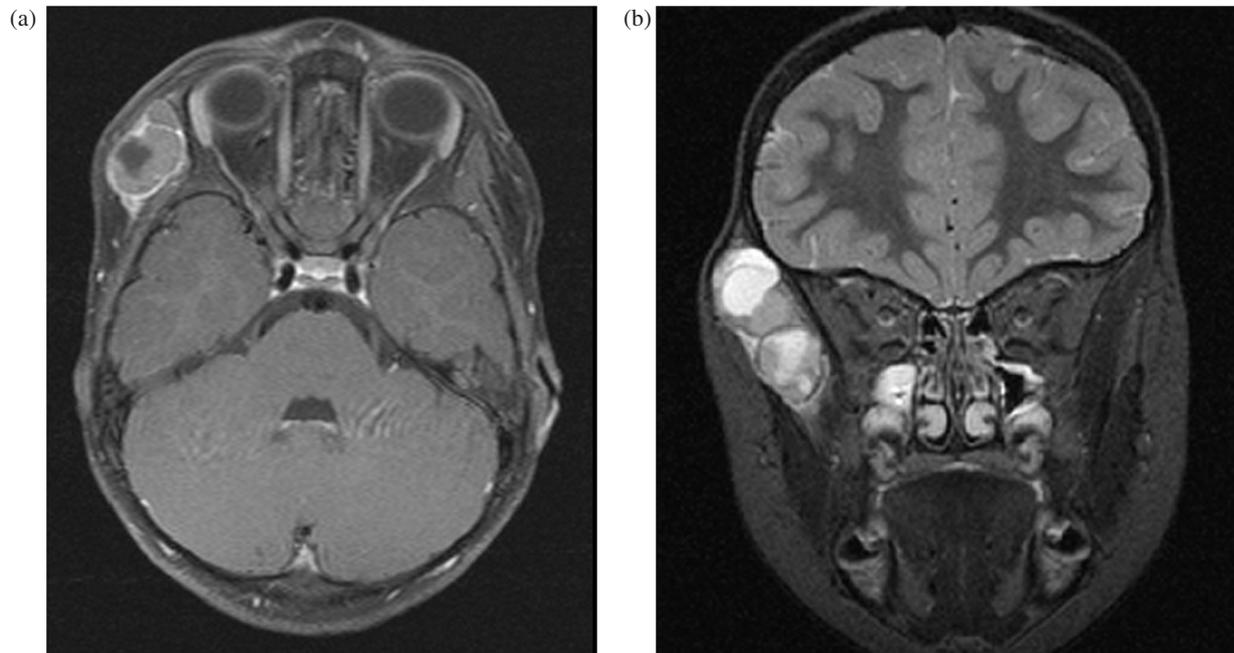


Figure 3 (a) Axial T1 weighted MRI of a right temporalis muscle RMS. (b) Coronal T2 weighted MRI of the same lesion.

also typically isointense or near isointense to muscle on T1 weighted images. Consequently, they are easily distinguished from benign lesions in the head and neck of children, for example, branchial cleft or thyroglossal duct cysts, which are generally of lower intensity than muscle on T1 images (Fig. 3a,b). Specific parameningeal sites include the nasal cavity, paranasal sinuses, pterygoid fossa, nasopharynx and middle ear (Fig. 4a,b).

Tumours at these locations tend to be large and invasive^[47]. Orbital tumours with intracranial invasion or bone destruction are also treated as parameningeal disease (Fig. 5). As surgery is often not feasible, all parameningeal tumours merit irradiation. From the information provided by imaging, the radiotherapist will include the full margins of the tumour plus a 2–3 cm margin^[48].

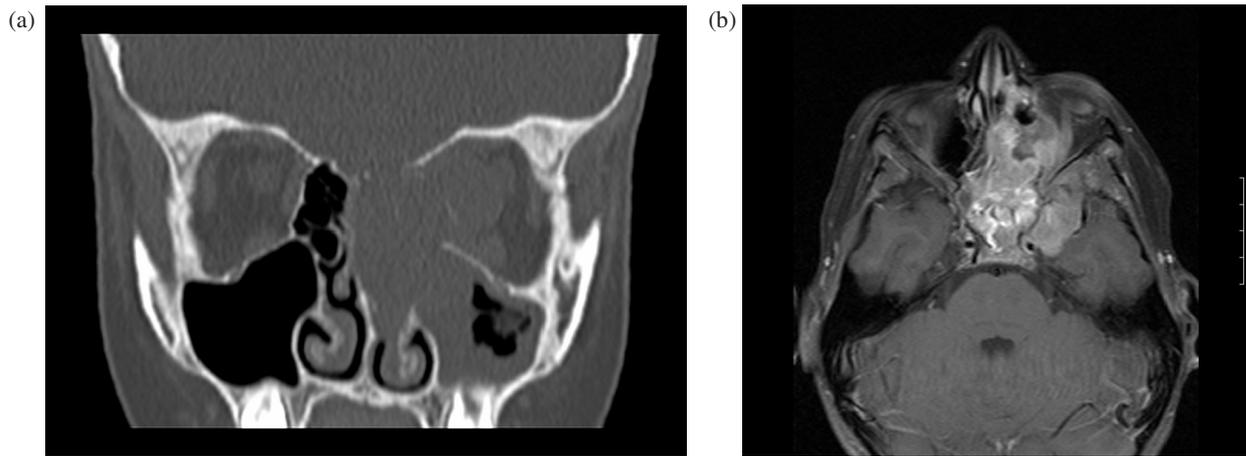


Figure 4 (a) Coronal CT of nasopharyngeal RMS extending into the left ethmoid and maxillary sinuses and the orbital fossa. (b) Axial T1 weighted MRI demonstrating intracranial extension of the tumour in the same patient.



Figure 5 Axial CT of a right orbital RMS extending through the infraorbital fossa.

In 2002 Simon *et al.*^[49] published survival data for head and neck RMS in a population of 140 patients. They reported a 5-year survival for patients 11 and > 11 years of $70 \pm 15\%$ and $36 \pm 25\%$, respectively.

A different approach, and less mutilating in the long term, is the use of the so-called AMORE technique^[50]. The AMORE protocol is a local treatment regimen for head and neck RMS (HNRMS) and consists of Ablative surgery, MOulage technique brachytherapy and surgical REconstruction. The aim of AMORE is to intensify local treatment for children with HNRMS and to avoid external beam radiation therapy and its

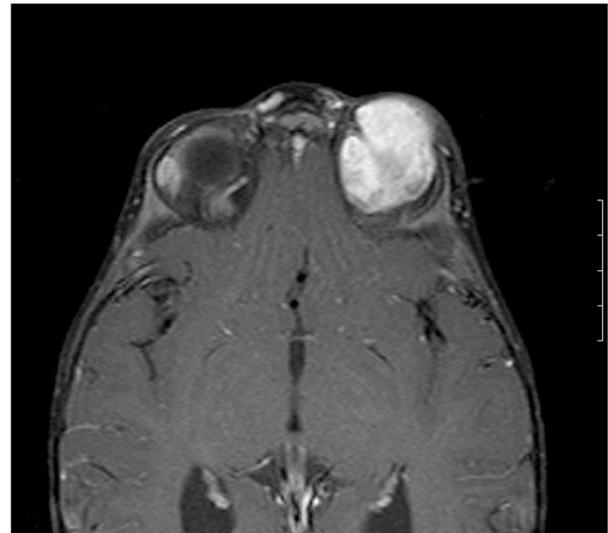


Figure 6 Axial T1 weighted fat-saturated MRI showing a left sided RMS confined to the orbit.

long term sequelae. Buwalda *et al.*^[51] reported on 22 patients who underwent the AMORE approach; of these, 7 showed relapse (6 within and 1 outside the tumour site)^[51].

Orbital RMS

Orbital RMS generally is non-invasive and confined to the bony orbit (Fig. 6). Tumour mass at presentation is commonly of similar size to the globe and the mass may be intra- or extra-conal^[52]. Regional lymph node extension is rare, believed to be due to a paucity of orbital lymphatics. Excellent survival rates in excess of 90% have been reported^[47]. When performing MRI of the orbit, fat saturation techniques are recommended to reduce the signal from normal orbital fat. Even for a site as favourable as the orbit, chemotherapy alone is generally not

sufficient in terms of local control or overall survival^[47]. Despite varied long term sequelae of local irradiation, combined radiation therapy and chemotherapy provide an excellent outcome and good quality of life.

RMS in the thorax and abdomen

Approximately 10% of RMS is truncal (Fig. 7). A few reports exist of RMS arising from congenital cystic lesions of the lung including cystic adenomatoid malformation but it is likely these alleged RMS tumours were actually pleuropulmonary blastomas rather than thoracic RMS^[53].

RMS is the most common pediatric tumour of the biliary tree, but is still very rare, accounting for only 1% of all RMSs. Ultrasound typically reveals biliary dilatation and a hilar mass. Associated portal vein thrombosis has not been described. A biliary origin however in a large hepatic tumour may be hard to prove as intraductal growth may not be obvious. The tumour may, in fact, arise from the intra- or extrahepatic bile ducts, the gallbladder or cystic duct, a choledocal cyst or the liver parenchyma^[42,54]. Extension into the duodenum is not uncommon. Unlike non-biliary RMS, in which complete excision is probably essential, complete excision in biliary RMS does not seem to be a prerequisite for long term survival and involvement of both right and left hepatic ducts is not a contraindication to surgery^[17,54]. US and MRI are required to show the tumour extent; if MRI is not available CT may be used. Metastases to the liver or peritoneal surfaces, including omentum, are also common. Intraperitoneal metastatic disease is seen in

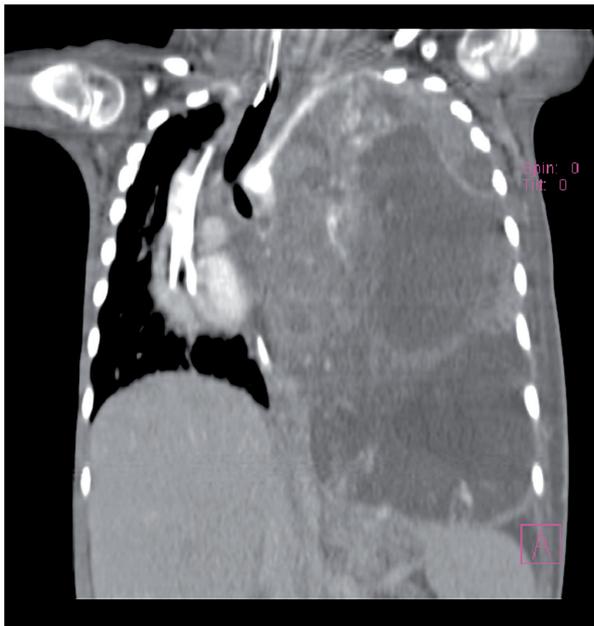


Figure 7 Coronal post-contrast CT showing a large, heterogeneously enhancing left thoracic RMS.

11% of children with RMS either at presentation or with later relapse.

Genitourinary RMS

Genitourinary (GU) RMS accounts for a quarter of all childhood RMS cases and RMS is the most common malignant neoplasm of the pelvis in children. Tumours in the bladder and prostate have a worse prognosis compared to other GU RMS. Prostatic tumours commonly spread laterally to the peri-urethral tissues and posteriorly to the perivesical tissues often invading the bladder base. Tumour extension can also occur superiorly and anteriorly to the bladder into the retroperitoneal space of Retzius^[55]. MRI in the coronal and sagittal planes, particularly T1 weighted sequences in which the urine within the bladder is hypointense, can give useful information on which to base clinical decisions (Fig. 8a,b). On T2 weighted sequences urine in the bladder can obscure hyperintense bladder wall tumour tissue. Fat-saturated T1 weighted images after gadolinium administration can usually define tumour extent initially. At the end of treatment, however, residual bladder wall thickening due to fibrosis can be extremely difficult to differentiate from residual tumour. A biopsy may be necessary and the role of PET-CT in this context is as yet unproven. The goal of therapy in bladder or bladder/prostate RMS is now survival with an intact and functioning bladder^[56].

Paratesticular RMS is applied to primary tumours arising in the spermatic cord, testis, epididymis and penis. Paratesticular RMS accounts for 7% of RMS and 12% of childhood scrotal tumours. The initial imaging investigation for any scrotal abnormality is ultrasound (US). US findings in RMS are non-specific, with similar findings being seen in more common paratesticular tumours such as fibromas, leiomyomas and adenomatoid tumours. Paratesticular RMS has variable echogenicity with a heterogeneous appearance due to haemorrhage and necrosis. They may show increased flow and low resistance on colour Doppler and may mimic infection. Abdominal CT imaging with both oral and intravenous contrast is merited in all these patients due to the high incidence of lymph node involvement^[42]. There has been a trend away from routine retroperitoneal dissection due to complications such as intestinal obstruction, loss of ejaculatory function and leg lymphoedema resulting in an increased reliance on CT to detect involved abdominal nodes. Reliance on CT with the omission of nodal sampling has, however, resulted in a higher relapse rate such that in North America sampling of ipsilateral lymph nodes is again advocated.

RMS in the extremities

MRI is particularly good for evaluating tumours arising in the limbs. Multiplanar imaging for assessment of tumour extent, neurovascular encasement and bone marrow

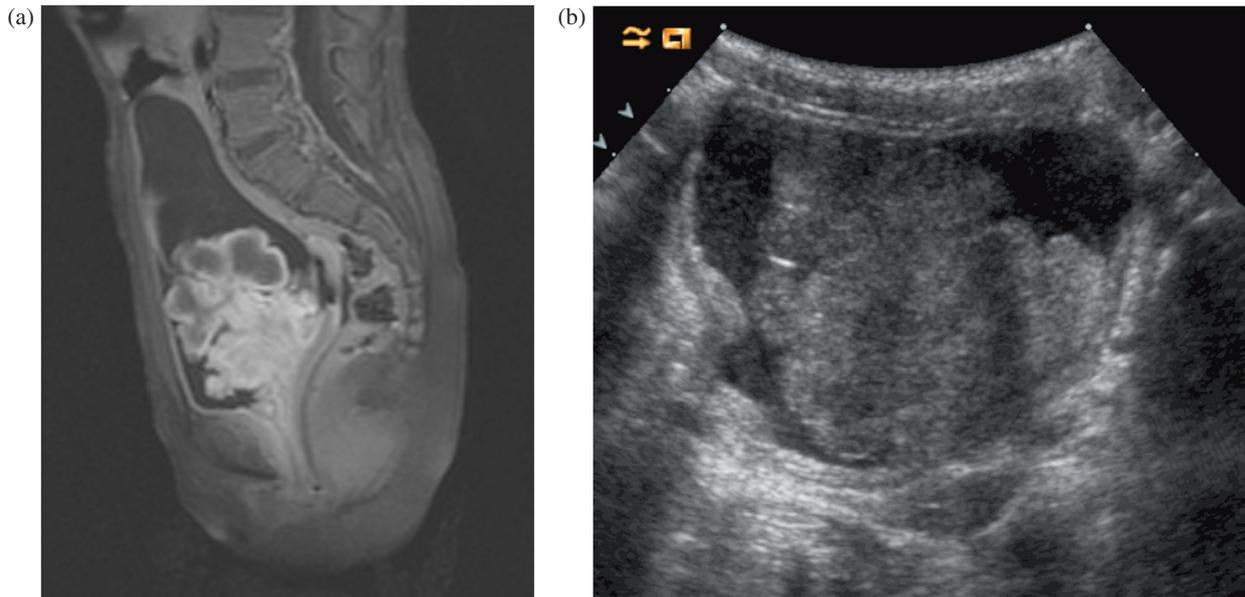


Figure 8 (a) Sagittal T1 weighted MRI of a bladder RMS with surrounding hypointense urine. (b) Ultrasound of the bladder in the same patient.

involvement and the higher inherent contrast resolution of MRI over CT make MRI the modality of choice when available. Fat suppressed sequences in a coronal plane can easily demonstrate tumour supero-inferior extent and regional lymphadenopathy. Unlike NRSTS, lymph node involvement is more frequent in extremity tumours than tumours at other sites^[57].

Imaging features in NRSTS

Synovial sarcoma

MRI is the modality of choice when evaluating synovial cell sarcoma, providing greater contrast between tumour and normal tissue than CT (Fig. 9). On MR the tumours tend to be sharply margined and may appear largely cystic which can lead to misdiagnosis as a haematoma, ganglion cyst, Baker's cyst, or other benign cystic mass. A mixed pattern of signal intensity described as the triple signal is seen in about a third of synovial sarcomas with high signal intensity similar to that of fluid, intermediate signal intensity iso- or slightly hyper-intense to fat and slightly lower signal intensity that resembles fibrous tissue. Fluid–fluid levels are seen in 18%. Tumours smaller than 5 cm have a homogeneously low signal intensity on T1 weighted sequences and marked heterogeneity on T2 weighted sequences. There is a variable degree of internal septation. About three-quarters of the tumours are intimately related to bone, with 50% abutting bone and 21% showing cortical thinning or medullary invasion. Approximately 30% of synovial sarcomas contain calcification^[58].

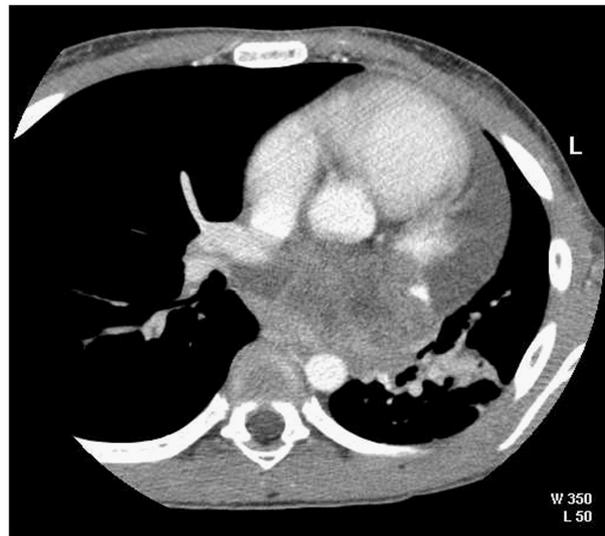


Figure 9 Contrast enhanced axial CT of a thoracic synovial cell carcinoma.

Fibrosarcoma

Congenital fibrosarcoma has very non-specific imaging appearances which reflect the non-aggressive behaviour of the lesion and may lead to incorrect diagnosis, for example, of a benign vascular malformation^[59]. The commonest radiographic finding is of a soft tissue mass, which may cause a mass effect leading to deformity of adjacent bony structures. Bone destruction is unusual and best assessed with CT. The fibrosarcoma itself is best imaged with MRI with medium signal intensity on T1 and high signal intensity on T2 weighted images

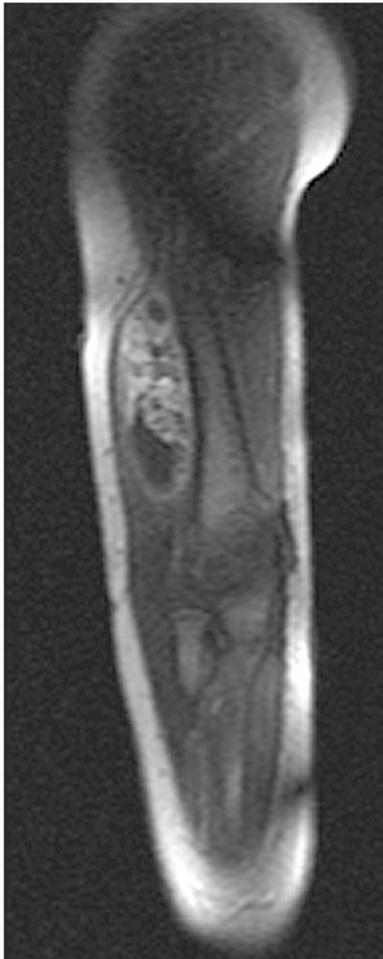


Figure 10 Coronal T1 weighted MRI of a congenital fibrosarcoma in the lateral compartment of the right thigh.

(Fig. 10). Areas of necrosis may be seen within it although homogenous appearances are also possible particularly with tumours in infancy. On US, a solid, vascular mass is seen^[60].

In fibrosarcoma, MRI shows a signal intensity close to that of muscle on T1 weighted images, a high signal intensity with some low signal areas on T2 weighted images, and not uncommonly, a non-homogeneous pattern of enhancing after the use of paramagnetic contrast agents^[61].

Malignant fibrous histiocytoma (MFH)

MRI typically reveals a well-defined intramuscular mass with heterogeneous signal intensity on all sequences. The signal intensity pattern is non-specific but usually low to intermediate on T1 weighted images and intermediate to high on T2 weighted images. Regions of fibrous tissue and calcification may be seen and solid components of the tumour typically reveal nodular and peripheral enhancement^[62].

Malignant peripheral nerve sheath tumours (MPNST)

Nerve sheath tumours have a low density on unenhanced CT images and on MRI are isointense to muscle on T1 weighted images and hyperintense on T2 weighted images with moderate to marked contrast enhancement^[63]. Unfortunately, the imaging features are not specific enough to distinguish benign nerve tumours from malignant, however, on T2 weighted MRI images, a 'target sign' with central hypointensity and a hyperintense rim is much more common in neurofibromas than MPNSTs^[64].

Biopsy: radiologically-guided or surgical?

The role of imaging-guided percutaneous core biopsy is a well-established method for diagnosis of malignancy in adults but is a more controversial area in the paediatric setting. The pathologist requires an adequate tissue sample to make the diagnosis and this must be balanced against a desire to be as minimally invasive as possible for the child's benefit. It is certainly possible to obtain adequate diagnostic tissue using needle biopsy, however, difficulties arise if the tumour is cystic or an insufficient sample is obtained^[65]. Biopsies in younger children are usually performed under general anaesthesia, and clinicians are reluctant to subject the child to another anaesthetic episode should the percutaneous biopsy fail to yield a diagnosis. For these reasons, many centres favour open surgical biopsy. However, image-guided biopsy with a 14G or 16G cutting needle usually gives adequate cores of tissue for paediatric biopsies. Ultrasound or CT guidance is used to avoid large vessels and cystic or necrotic areas of tumour which improves diagnostic yield and decreases risk of haemorrhage. Diagnostically adequate samples are obtained in 94% of cases^[66]. Close cooperation with the local histopathology department is required. Fine needle aspiration cytology is unreliable, particularly at initial diagnosis, and should therefore be avoided.

Complications of treatment

The spectrum of abnormalities detected in patients treated for childhood cancer has broadened with the use of new and more sensitive imaging modalities, notably MRI, and improvements in long term survival with an unfortunate increased risk of second malignancy^[67]. Multimodal treatment plans have improved survival rates in patients with STS, however, this success comes with a toll. Increased survival rates are accompanied by more late term effects of treatment, either due to surgery itself or to the effects of radiotherapy or chemotherapy. Children with head and neck soft tissue sarcomas develop radiotherapy related problems in the majority of cases including cataracts, orbital hypoplasia,

facial growth retardation, neuroendocrine dysfunction, dental abnormalities, hypothyroidism, intellectual and academic delay and the development of second malignancies^[22,42]. Bowel obstruction (12%), haemorrhagic cystitis (33%) and an increase in follicle stimulating hormone were apparent in 84 patients who underwent treatment for paratesticular RMS. Of 109 patients treated for bladder/prostate tumours, 50% lost their bladders, 10% had growth retardation and 29% had abnormal findings on renal imaging^[42]. There are many side effects associated with chemotherapy both acutely such as immunosuppression and sepsis, hair loss, nausea and vomiting and veno-occlusive disease and more long term effects such as loss of ovarian or spermatogenic function and peripheral neuropathy.

Radiation induced bone changes can be demonstrated radiologically and include radiation osteitis, impairment of bone growth including injury to the epiphyseal plate, osteonecrosis, medullary infarction and osteochondromas.

Post-surgical changes in anatomy can be radical, due to resection and soft-tissue transplants, and may make interpretation cumbersome. A comprehensive understanding of the surgical procedure is essential for the interpretation of follow-up imaging.

The future

The aims for the future management of children with STS must necessarily be focused on increasing survival rates whilst reducing long term morbidity. Ongoing multi-centre international trials allow new or adjusted treatment protocols to be assessed in large enough populations for useful information to be obtained as to their efficacy. As well as this, the results from these trials combined with refinements in pathological, biological and genetic assessments may lead to improvements in risk assignment, allowing any chemotherapeutic or radiotherapy regimes to be targeted to subgroups of patients who will obtain a real benefit from the treatment. The decision by the EpSSG to adopt the North American IRS grouping system of patients at diagnosis will allow studies on both sides of the Atlantic to be directly comparable.

This is particularly important in those patients with high-risk metastatic disease and those who develop tumour recurrence, in whom overall survival has remained disappointingly low with little improvement over the last 15 years^[68]. Despite aggressive multimodality treatments, only 25% are expected to be disease free 3 years after diagnosis. A better understanding of biological differences as well as new active agents are needed to improve outcome. Review of prognostic factors in children with metastatic disease has identified subsets of patients with a more favourable outcome and has allowed protocol modification. For example, risk assessment data from IRS-IV has led to new protocols for IRS-V reducing

exposure to cyclophosphamide and radiotherapy in patients at low risk while adding new, active agents such as toptotecan or irinotecan to the standard therapy for patients with unfavourable histology or advanced disease.

In terms of radiology, MRI and CT will continue to be of major importance in diagnosis, staging, radiotherapy planning and follow-up of children with STS. Ongoing improvements in image quality may also lead to further improvements in accuracy of staging.

Positron emission tomography (PET) is being increasingly used in oncological assessment. PET provides metabolic information to supplement morphological or anatomical imaging and can be useful in a number of ways; in the distinction of benign from malignant tumours, in distinguishing scar tissue from residual neoplasm in children who have completed therapy or in detecting regression of metabolic tumour activity, which may serve as a surrogate for tumour response^[69]. No large studies to date have specifically looked at the use of PET in paediatric STS patients but results from small patient series suggest it may play a role in the staging of RMS and in the detection of recurrence^[70]. PET is likely to play a part in the future management of childhood STS. A negative PET-CT study at trial entry likely confirms the absence of metastatic disease for example.

Other strategies being considered for the future include the identification of new treatment targets through gene-expression and the use of CpG oligopeptides, oncolytic herpes simplex virus tumour injections, rapamycin analogues, vaccines against small tumour peptide fragments, epidermal growth factor receptor tyrosine kinase inhibitors, and tumor necrosis factor alpha-related apoptosis-inducing ligands (TRAILs). All of these promise to provide opportunities for novel interventions for patients with STS^[24].

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